FORM PTO-1390 (Modified) (REV 11-98) U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE

TRANSMITTAL LETTER TO THE UNITED STATES DESIGNATED/ELECTED OFFICE (DO/EO/US) CONCERNING A FILING UNDER 35 U.S.C. 371

ATTORNEY'S DOCKET NUMBER	U.S. APPLICATION NO. (IF KNOWN, SEE 37 CFR)
ABLE-0014	09/530375

INTERNATIONAL APPLICATION NO.	INTERNATIONAL FILING DATE	PRIORITY DATE CLAIMED
PCT/GB98/03317	5 November 1998	7 November 1997

TITLE OF INVENTION
SKIN PENETRATION ENHANCING COMPONENTS

APPLICANT(S) FOR DO/EO/US
ORMEROD, Anthony and WINFIELD, Arthur

Applicant herewith submits to the United States Designated/Elected Office (DO/EO/US) the following items and other information:

1. ☒ This is a **FIRST** submission of items concerning a filing under 35 U.S.C. 371.
2. ☐ This is a **SECOND** or **SUBSEQUENT** submission of items concerning a filing under 35 U.S.C. 371.
3. ☐ This is an express request to begin national examination procedures (35 U.S.C. 371(f)) at any time rather than delay examination until the expiration of the applicable time limit set in 35 U.S.C. 371(b) and PCT Articles 22 and 39(1)
4. ☒ A proper Demand for International Preliminary Examination was made by the 19th month from the earliest claimed priority date.
5. ☒ A copy of the International Application as filed (35 U.S.C. 371 (c) (2))
   a. ☐ is transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☒ has been transmitted by the International Bureau.
   c. ☐ is not required, as the application was filed in the United States Receiving Office (RO/US)
6. ☐ A translation of the International Application into English (35 U.S.C. 371(c)(2)).
7. ☒ A copy of the International Search Report (PCT/ISA/210).
8. ☒ Amendments to the claims of the International Application under PCT Article 19 (35 U.S.C. 371 (c)(3))
   a. ☐ are transmitted herewith (required only if not transmitted by the International Bureau).
   b. ☐ have been transmitted by the International Bureau.
   c. ☐ have not been made; however, the time limit for making such amendments has NOT expired
   d. ☒ have not been made and will not be made.
9. ☐ A translation of the amendments to the claims under PCT Article 19 (35 U.S C. 371(c)(3)).
10. ☐ An oath or declaration of the inventor(s) (35 U.S.C. 371 (c)(4)).
11. ☒ A copy of the International Preliminary Examination Report (PCT/IPEA/409).
12. ☐ A translation of the annexes to the International Preliminary Examination Report under PCT Article 36 (35 U.S.C. 371 (c)(5)).

Items 13 to 20 below concern document(s) or information included:

13. ☒ An Information Disclosure Statement under 37 CFR 1.97 and 1.98.
14. ☐ An assignment document for recording. A separate cover sheet in compliance with 37 CFR 3.28 and 3.31 is included.
15. ☒ A **FIRST** preliminary amendment.
16. ☐ A **SECOND** or **SUBSEQUENT** preliminary amendment.
17. ☐ A substitute specification.
18. ☐ A change of power of attorney and/or address letter.
19. ☐ Certificate of Mailing by Express Mail
20. ☐ Other items or information:

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By Deborah Ehret
Typed Name: Deborah Ehret

U.S APPLICATION NO. (IF KNOWN, SEE 37 CFR	INTERNATIONAL APPLICATION NO	ATTORNEY'S DOCKET NUMBER
09/530375	PCT/GB98/03317	ABLE-0014

21. The following fees are submitted:.

BASIC NATIONAL FEE (37 CFR 1.492 (a) (1) - (5)) :

		CALCULATIONS PTO USE ONLY
☐	Neither international preliminary examination fee (37 CFR 1.482) nor international search fee (37 CFR 1.445(a)(2) paid to USPTO and International Search Report not prepared by the EPO or JPO **$970.00**	
☒	International preliminary examination fee (37 CFR 1 482) not paid to USPTO but Internation Search Report prepared by the EPO or JPO **$840.00**	
☐	International preliminary examination fee (37 CFR 1.482) not paid to USPTO but international search fee (37 CFR 1.445(a)(2)) paid to USPTO **$690.00**	
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) but all claims did not satisfy provisions of PCT Article 33(1)-(4) **$670.00**	
☐	International preliminary examination fee paid to USPTO (37 CFR 1.482) and all claims satisfied provisions of PCT Article 33(1)-(4) **$96.00**	
	ENTER APPROPRIATE BASIC FEE AMOUNT =	**$840.00**
	Surcharge of **$130.00** for furnishing the oath or declaration later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (e)).	**$0.00**

CLAIMS	NUMBER FILED	NUMBER EXTRA	RATE	
Total claims	16 - 20 =	0	x $18 00	**$0.00**
Independent claims	2 - 3 =	0	x $78.00	**$0.00**
Multiple Dependent Claims **(check if applicable)**.			☐	**$0.00**
	TOTAL OF ABOVE CALCULATIONS =			**$840.00**
	Reduction of 1/2 for filing by small entity, if applicable. Verified Small Entity Statement must also be filed (Note 37 CFR 1.9, 1.27, 1.28) **(check if applicable)**. ☐			**$0.00**
	SUBTOTAL =			**$840.00**
	Processing fee of **$130.00** for furnishing the English translation later than ☐ 20 ☐ 30 months from the earliest claimed priority date (37 CFR 1.492 (f)). +			**$0.00**
	TOTAL NATIONAL FEE =			**$840.00**
	Fee for recording the enclosed assignment (37 CFR 1.21(h)). The assignment must be accompanied by an appropriate cover sheet (37 CFR 3.28, 3.31) **(check if applicable).** ☐			**$0.00**
	TOTAL FEES ENCLOSED =			**$840.00**
				Amount to be: refunded $
				charged $

☒ A check in the amount of **$840.00** to cover the above fees is enclosed.

☐ Please charge my Deposit Account No. in the amount of to cover the above fees.
A duplicate copy of this sheet is enclosed.

☒ The Commissioner is hereby authorized to charge any fees which may be required, or credit any overpayment to Deposit Account No. **12-1086** A duplicate copy of this sheet is enclosed.

NOTE: Where an appropriate time limit under 37 CFR 1.494 or 1.495 has not been met, a petition to revive (37 CFR 1.137(a) or (b)) must be filed and granted to restore the application to pending status.

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32,257
REGISTRATION NUMBER

27 April 2000
DATE

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: **ABLE-0014**

Inventors: **ORMEROD AND WINFIELD**

International Application No.: **PCT/GB98/03317**
U.S. Serial No.: **N/A**

International Filing Date:
U.S. Filing Date: **HEREWITH**

Title: **SKIN PENETRATION ENHANCING COMPONENTS**

"Express Mail" Label No. EL638154317US
Date of Deposit: APRIL 27, 2000

I hereby certify that this paper is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to the Assistant Commissioner for Patents, Box PCT, Washington, D.C. 20231.

By Deborah Ehret
Typed Name: DEBORAH EHRET

Assistant Commissioner for Patents
Box PCT
Washington, D.C. 20231

Dear Sir:

PRELIMINARY AMENDMENT

Please amend the above-referenced application as follows:

IN THE CLAIMS:

Please cancel claims 1-23 and replace with the following new claims:

--24. A topical formulation for the treatment of a dermatological condition which comprises a macrocyclic lactone antibiotic, immunosuppressive macrolide or a pharmacologically active analogue, derivative or pro-drug thereof and a permeation modulator which are present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

25. The formulation of claim 24 comprising up to 10% by weight of the macrocyclic lactone antibiotic or the immunosuppressive macrolide or analogue, derivative or pro-drug thereof and 1 to 60% by weight of the permeation modulator.

26. The formulation of claim 24 wherein the macrocyclic lactone antibiotic is erythromycin, azithromycin or clarithromycin.

27. The formulation of claim 24 wherein the immunosuppressive macrolide is sirolimus, FK506 or SDZ ASM 981.

28. The formulation of claim 24 wherein the permeation modulator is an alkanoic acid or alkenic acid.

29. The formulation of claim 24 wherein the alkanoic acid or alkenic acid is capric acid, octanoic acid or oleic acid.

30. The formulation of claim 24 wherein the dermatological condition is psoriasis, alopecia, eczema dermatitis, lichen planus, lupus erthematosus, pyoderma gangrenosum, vitiligo, graft versus host disease, pustular skin infections, bacterial skin infections or acne vulgaris.

31. The formulation of claim 30 wherein the dermatological condition is eczema dermatitis and the concentration of macrocyclic lactone antibiotic or immunosuppressive macrolide is 0.05% to 2% by weight.

32. The formulation of claim 24 wherein the permeation modulator is used in conjunction with a solvent system.

33. The formulation of claim 32 wherein the solvent system comprises an aromatic alcohol or a biologically acceptable benzene derivative, with or without an admixture of monoglycerides and a fatty acid ester.

34. The formulation of claim 32 wherein the solvent system comprises an aromatic alcohol or a biologically acceptable benzene derivative, with or without an admixture of a fatty acid ester.

35. The formulation of claim 32 wherein the permeation modulator comprises capric acid and the solvent system comprises benzyl alcohol.

36. The formulation of claim 32 wherein the concentration of the solvent system is 5% to 90% by weight.

37. The formulation of claim 24 further comprising a thickening agent.

38. The formulation of claim 37 wherein the thickening agent is white soft paraffin, cetostearyl alcohol, yellow soft paraffin, cetyl alcohol, steryl alcohol, divalent carboxylic acid soaps or carnauber wax.

39. A method for the treatment of a dermatological condition comprising administering an effective amount of the topical formulation of claim 24.--

REMARKS

The pending claims in PCT/GB98/03317 have been canceled and replaced with new claims 24-39 to conform the claims to U.S. practice for entry into National Phase. No new matter has been added by this amendment.

Respectfully submitted,

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Date: April 27, 2000

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SKIN PENETRATION ENHANCING COMPONENTS

This present invention relates to an effective treatment for psoriasis and other dermatological conditions using a topically applied immunosuppressive agent. The preferred formulation does not allow the agent to appear in the blood or other circulatory system at any significant level.

Dermatological conditions can be uncomfortable and embarrassing for the patient, so an effective safe treatment is required. Some dermatological conditions are caused by an overactive immune system, examples are psoriasis, alopecia, lichen planus, lupus erythematosus, pyoderma gangrenosum, vitiligo and graft versus host disease. Others can be due to bacterial or pustular skin infections.

Dermatological conditions caused by an overactive immune system can be treated by immunosuppressive macrolides, for example sirolimus (rapamycin), FK-506 (tacrolimus) or SDZ ASM 981. Those that are caused by bacteria or are deeper skin infections, such as acne vulgaris and hidranitis suppcurativa, can be treated by macrolide antibiotics, for example erythromycin, azithromycin and clarithromycin. The above agents may be applied by means of topical creams and lotions or taken orally.

Psoriasis affects 2.4% of the population and the current understanding of the pathogenesis of the disease is that it is driven initially by immunocytes. These and keratinocytes are mutually stimulated and activated through the production of cytokines, TGFa, IL-6 and IL-8 from lymphocytes. This leads to a hyperproliferative epidermis with rapid 36 hour cycling of the transient amplifying compartment of

keratinocytes.

FK506 is a macrolide antibiotic which shows part homology with sirolimus. Research in models has shown that it has some efficacy in the topical therapy of contact dermatitis, atopic eczema and to a lesser degree psoriasis. Cyclosporin is also known to be effective in treating a wide range of skin diseases. However the usefulness of these drugs is limited by their potential side effects resulting from systemic administration.

Other forms of treatment of dermatological conditions may include using topical steroids but these have undesirable effects such as irreversible atrophy and purpura.

In the treatment of the human or animal body, one of the considerations is that any medicament shall as far as possible affect only the afflicted part. It is well known that amounts of circulating drug should be kept as low as possible to avoid unwanted mutations. A problem with the topical application of medicaments to the skin for example, is that the medicament tends to penetrate the skin and establish itself in the circulating blood system. This is not what is intended in the treatment of dermatological conditions.

The macrocyclic lactone antibiotic rapamycin for example as disclosed in EP-A-0533433 has already been used topically to treat such skin disorders as psoriasis and dermatitis. However no attempt has been made to reduce the amount of rapamycin translocated across the skin into the systemic system. Nor is there any discussion of the reduction of the levels of circulating rapamycin or other macrolide drug at the same time as providing therapeutically effective treatment for

a variety of skin disorders.

We have now found that this may be achieved by the addition to such drugs of a permeation modulator. Permeation enhancers are well known as a class of drug translocation facilitors, but the purpose of these is to increase the drug flux across the skin. A permeation modulator however has the facility to allow the drug to penetrate the skin, and particularly the stratum corneum, without significantly passing through the epidermis into systemic systems (eg the blood or lymph systems).

It is also known that immunosuppressive agents taken orally and steroids applied topically can be used to treat dermatological conditions, such as psoriasis or eczema. However, they are often non-specific in their action which leads to undesirable side effects. Thus it would be desirable to develop a topical delivery formulation for an immunosuppressive agent which preferentially treats the diseased sites only and avoids significant systemic exposure; so reducing harmful side effects.

Sirolimus is a macrocyclic lactone antibiotic produced by the organism *Streptomyces hygroscopicus;* it is known to have potent immunosuppressive activities. Sirolimus acts through specific binding of a family of cytosolic immunophilins called the FK binding proteins (FKBP). The sirolimus FKBP complex acts at least three sites. Firstly, by blocking the phosphorylation activation of p70 s6 kinase, an enzyme acting on the 40S ribosomal subunit s6 protein, thereby reducing the efficiency of translation. Secondly by preventing activation of specific elongation factors required for protein synthesis. Thirdly, it inhibits enzyme activity of the cyclin dependent

kinase cdK-cyclin E complex which forms one of the tight controls of the G1/S transition in cell division by inhibiting the normal decline of the p27 cdk inhibitor which would follow IL-2 stimulation. Sirolimus has an advantage over other immunosuppressive agents in the treatment of psoriasis as it has an inhibitory effect on keratinocyte proliferation. *In vitro* experiments have shown that this inhibitory effect takes place at concentrations ranging from 3-10μg/ml. A broader range may be employed for example 1 to 20μg/ml, but the more efficacious range is 5-8μg/ml.

According to the first aspect of the invention, there is provided a topical formulation for the treatment of a dermatological condition which comprises a macrocyclic lactone antibiotic or immunosuppressive macrolide or a pharmacologically active analogue, derivative or pro-drug thereof; characterised in that it further comprises a permeation modulator and the permeation modulator and the macrocyclic lactone antibiotic, immunosuppressive macrolide or pharmacologically active analogue, derivative or pro-drug are present in relative amounts such that when a therapeutic amount is applied to the skin, a minimal systemic effect is produced.

By the term "minimal systemic effect", is meant that the amount of active principal detectable in the blood stream is preferably less than 0.3 ng/nl over 4 to 24 hours after administration, more preferably below 0.1 ng/ml over the same period.

Preferably the macrocyclic lactone antibiotic is selected from erythromycin, azithromycin or clarithromycin. These macrocyclic lactone antibiotics are effective for treating

pustular and bacterial skin infections such as acne vulgaris.

Conveniently the immunosuppressive macrolide is selected from sirolimus, FK-506 or SDZ ASM 981. Sirolimus is a favoured alternative because it is also an effective antibiotic which is useful in the microbiological preservation of the formulation. The microbiological properties of sirolimus are also helpful in the treatment of scalp and flexural psoriasis, seborrhoeic dermatitis and in secondarily atopic eczema.

In preferred embodiments the permeation modulator may be an alkanoic or alkenic acid, preferably having 6 to 20 carbon atoms such as capric acid, octanoic acid, oleic acid or acids or such acids of intermediate chain length. The permeation modulator aids the penetration of the immunosuppressive macrolide or macrocyclic antibiotic through the stratum corneum, the principle barrier to the penetration of drugs. The stratum corneum is an aggregate of the stacked, flattened skeletons of keratin filled cells interspersed with lipid monolayer structures and water. The addition of the permeation modulator to the formulation results in the partial disruption of the barrier components, particularly the lipid structures. A gradient of the drug can then be produced across the stratum corneum particularly, which facilitates the diffusion of the immunosuppressive macrolide or macrocyclic lactone antibiotic across the stratum corneum into the living epidermis. The relative concentrations of the macrolide or antibiotic and the permeation modulator are chosen so that only partial penetration of the skin occurs; the macrocyclic lactone antibiotics or immunosuppressive macrolides reach the areas which require treatment but significant absorption of the said drugs into the systemic circulation is avoided thus reducing the likelihood of any systemic side effects.

Conveniently the permeation modulator is used in conjunction with a solvent system which includes an aromatic alcohol such as phenyl-alkanol or a biologically acceptable benzene derivative, with or without an admixture of monoglycerides and/or a fatty acid ester (e.g. isopropyl myristate). Other solvents used, include benzaldehyde, benzyl benzoate and acetone. The combination of solvent and permeation modulator further optimises the passage of the immunosuppressive macrolide or the macrocyclic lactone antibiotic across the stratum corneum.

Preferably, the concentration of the macrocyclic lactone antibiotic or immunosuppressive macrolide is up to 10% by weight of the formulation. More preferably the concentration of the macrocyclic lactone antibiotic or immunosuppressive macrolide is either 0.5% to 5.9% or 6% to 12% by weight. Even more preferably the concentration of the macrocyclic antibiotic or immunosuppressive macrolide is either 1 to 5% or 6 to 8% by weight. A concentration of 0.05% to 2% is most preferable in the treatment of eczema. The term "% by weight" used herein refers to the "% by weight of the final formulation".

Preferably the above ranges of macrocyclic lactone antibiotic or immunosuppressive macrolide or analogue derivative or pro-drug thereof are used in an agent comprising a permeation modulator; wherein the concentration of the permeation modulator is 0.1% to 60% by weight. More preferably the concentration of the permeation modulator is either 0.1% to 39.9% or 40% to 80% by weight. Even more preferably the concentration of the permeation modulator is either 0.1% to 19.9%, 20% to 39.9% or 40% to 60%.

Preferably the above ranges of macrocyclic lactone antibiotic or immunosuppressive and permeation modulator are used in a formulation in conjunction with a solvent system; wherein the concentration of the solvent system is 5% to 90% by weight. More preferably the concentration of the solvent system is either 0.1% to 49.9% or 50% to 90% by weight. Even more preferably the concentration of the solvent system is either 0.1% to 19.9%, 20% to 39.9%, 40% to 69.9% or 70% to 90% by weight.

Preferably a thickening agent is present in the formulation. If the formulation is to be used topically, it should be of an appropriate consistency. Therefore, thickening agents such as cetostearyl alcohol or commercially available medical grade white soft paraffin may be added. These can reduce the penetration of the immunosuppressive agent but they are required for effective application. The formulations of the invention are particularly suitable for treatment of conditions of the scalp.

In addition to the liquid and solid vehicles set forth above, the formulations of the invention may additionally include one of the following:- flavouring agents, lubricants, solubilizers, suspending agents, filler and glidants.

The formulation can also be dissolved or suspended in any pharmaceutically acceptable liquid carrier or vehicle such as water or a pharmaceutically acceptable oil or fat. Such a liquid carrier or vehicle can contain other pharmaceutically acceptable additives such as solubilizers, emulsifier, buffers, preservatives, suspending agents, thickening agents, colouring agents, viscosity regulators, stabilizers or osmo-regulators.

The invention will now be described, by way of illustration only, with reference to the following examples, tables and figures accompanying the specification

Figure 1 is a graphical representation of the effect on the flux (µg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the capric acid and benzyl alcohol ratio, where x is the percentage of capric acid in the benzyl alcohol.

Figure 2 is a graphical representation of the effect on the flux (µg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the octanoic acid and benzyl alcohol ratio, where x is the percentage of octanoic acid in the benzyl alcohol.

Figure 3 is a graphical representation of the effect on the flux (µg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the oleic acid and benzyl alcohol ratio, where x is the percentage of oleic acid in the benzyl alcohol.

Figure 4 is a graphical representation of the effect on the flux (µg/hr/cm^2) of sirolimus (y) through the stratum corneum by varying the sirolimus concentration (mg/ml) (x) while keeping the capric acid to benzyl acid ratio constant.

Figure 5 is a graphical representation of the results of the clinical score (y) determined after application of the sirolimus formulation ( ) and the control (::::) in Example 3.

Figure 6 is a graphical representation of the difference in the clinical score after application with sirolimus formulation in Example 3, where y is the number of subjects

in each group. A positive score (x) shows improvement with use of the active formulation.

Figures 1 to 4 were obtained by *in vitro* experimentation. The results were used to optimize the sirolimus concentration and the ratio of permeation enhancer and solvent used in *in vivo* experiments.

Example 1

A formulation was formed of 8% sirolimus and 92% of a vehicle of capric acid (50%) with benzyl alcohol (50%). This was tested in single application experiments on four individuals with normal skin. Venous blood samples were taken at 4, 7 and 24 hours after application and no significant levels of sirolimus were detected using MSGCMS, which is able to detect sirolimus levels down to 0.1ng/ml.

In parallel, skin biopsies were taken from the individuals after 7 hours, the biopsy samples were glued to a glass slide and serially sectioned horizontally into 4 layers each 0.7mm thick and extracted with acetonitrile. The results are given in Table 1.

Table 1 shows the tissue concentrations of sirolimus 7 hours after application of capric acid: benzyl alcohol (50:50) containing sirolimus at 8%. The horizontal skin sections were each 0.7mm. Accordingly, for example, the section of skin designated 2 was the horizontal layer of skin 0.7-1.4mm from the surface of the skin.

Section of skin 1=surface	Sirolimus concentration μg/mg			
	A	B	C	D
1	0.059	0.288	0.301	0.216
2	Not done	0.108	0.144	0.126
3	0.255	0.173	0.339	0.256
4	0.239	0.214	0.370	0.241

Example 2

A formulation of sirolimus (2.2%) in a vehicle comprising isopropyl myristate 40%, benzyl alcohol 10% and capric acid 50% was tested in single application experiments on three individuals with normal skin. Venous blood samples were taken at 4, 7 and 24 hours after application and no significant levels of sirolimus were detected using MSGCMS.

After 7 hours biopsy samples were taken from two of the individuals. These were bisected in parallel with the surface to give an upper and lower half, roughly corresponding to the epidermis and dermis. The skin was homogenised with acetonitrile and sirolimus concentration was determined by HPLC. The results are given in Table 2

Table 2 shows the tissue concentrations of sirolimus 7 hours after application of capric acid: isopropyl myristate: benzyl alcohol (50:40:10) containing sirolimus at 2.2%.

Level of skin segment	Sirolimus Concentration μg/mg	
	Subject A	Subject B
Upper (1)	0	1.5
Lower (2)	0.333	0.5

Example 3

A double blind, left-right comparison of the effect of applying topical sirolimus in formulations as described in Examples 1 and 2, to 24 patients with chronic (over three months) plaque psoriasis was conducted. (22 out of the 24 patients were eventually analysed.) A single target plaque was treated for the first 6 weeks with the lower potency formulation of Example 2. After this the active treatment was increased to the higher potency formulation of Example 1 for 6 weeks unless a clear improvement on one side had already occurred.

The study included adults with stable, clearly demarcated, chronic plaque psoriasis, and two, well matched, contralateral, comparable plaques about 50cm^2 in area on opposite sides of the body. Subjects were all aged over 18 years, were able to apply creams and had no other significant medical problems. Transaminases were not more than twice the upper limit of normal and subjects were selected to avoid those likely to have a holiday in sunlight during the 6-12 weeks of the trial.

Before the trial started, there was a two week washout period in which only bland emollients were applied to the target lesions.

Treatment was randomised and double blind. Hands were thoroughly washed between the twice daily application of the test formulations. The active formulation was applied consistently to one plaque while a control comprising only the vehicle base was applied consistently to the plaque on the opposite side. Where possible the arms or elbows were selected as target areas as cross contamination is less likely at these

sites.

Assessments were done at weeks 0, 2, 4 and 6 on the low potency treatment and at 8,10 and 12 on the higher dose formulation, provided there were no signs or laboratory evidence of toxicity. Clinical scoring was done at each attendance and areas traced at the start and finish of treatment. Biopsies from active and control lesions were performed at the end of treatment or at withdrawal. Biopsies were not done if an adverse event such as a reaction to the application occurred as this would influence the measures being assessed.

The lesions were also assessed at fortnightly intervals with subjective scoring on a scale of 0-8 for erythema, thickening, and scaling. Objective measures of improvement were performed on both lesions at the end of each treatment period (low and high formulations). These included pulsed A scan ultrasound measurement of lesion thickness and erythema measured with a reflectance erythema metre, both were averaged over 5 areas in each psoriatic lesion and were validated using a previous study which was performed using betamethasome as a reference.

At each visit we measured the full blood count, biochemistry, including urea, electrolytes, liver enzymes, bilirubin, calcium, magnesium, uric acid, glucose, amylase, muscle enzymes, lipids and cholesterol. Sirolimus levels were performed every 2 weeks during therapy. Samples for sirolimus levels were stored at minus 80° C and shipped to a central reference laboratory for analysis by LC/MS/MS by Wyeth Ayerst Research.

In biopsies, epidermal thickness was measured and

immunoperoxidase immunohistochemistry done using the following antibodies to count cells in a blinded fashion:

Thus, antibody Ki-67 was used to give a measure of hyperproliferation in the epidermis and CD4 helper lymphocytes were used to give a measure of auto-immune activity which drives psoriasis.

Cell counting in tissues was automated, using computer assisted image analysis (Seescan). Data was analysed by Student's T test for paired data and Wilcoxon's test.

Comparison of the final scores, active vs placebo achieved significance at 0.032 by T test or Wilcoxon's test 0.0457, see Table 3 and Figures 5 and 6. The erythema measurements and ultrasound recordings were not significantly different. Three of the twenty-two patients developed contact sensitivity to the topical preparations one to benzyl alcohol, one to sirolimus and one to both of these.

The antibody tests with Ki-67 showed a significant reduction of proliferating cells from a mean of 83/mm^3 in control to 55/mm^3 with Sirolimus (rapamycin) to give a significance of P-0.027 (T test). Using CD4 cells control values were 61/mm^3 against 32.7/mm^3 means values following rapamycin to give a significance of P-0.0026 (T-test). The T-test were unpaired due to missing samples.

Table 3 shows the clinical response to topical sirolimus. The clinical score is measured on a scale of 0-24 with higher values indicating a better result, ultrasound thickness in mm and erythema measurement in arbitrary units.

	Sirolimus		Control		Significance
	Mean	S.D.	Mean	S.D.	
Clinical Score	11.2	5.8	9.1	4.8	p=0.032
Ultrasound thickness	2.99	0.6	2.96	0.72	NS
Erythema measurement	34.5	7.9	33.1	7.7	NS

These results show that penetration of sirolimus from a formulation described above does occur. It is thought that increased adsorption would occur through the scalp to effectively treat scalp psoriasis.

CLAIMS:

1. A topical formulation for the treatment of a dermatological condition which comprises a macrocyclic lactone antibiotic, immunosuppressive macrolide or a pharmacologically active analogue, derivative or pro-drug thereof; characterized in that it further comprises a permeation modulator and the permeation modulator and the macrocyclic lactone antibiotic or macrolide or the pharmacologically active analogue, derivative or pro-drug thereof are present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

2. A formulation according to claim 1 comprising up to 10% by weight of the macrocyclic lactone antibiotic or the immunosuppressive macrolide or analogue, derivative or pro-drug thereof; the permeation modulator being present at 1 to 60% by weight.

3. A formulation according to either claim 1 or 2 wherein the macrocyclic lactone antibiotic is selected from erythromycin, azithromycin or clarithromycin.

4. A formulation according to either claim 1 or 2 wherein the immunosuppressive macrolide is selected from sirolimus, FK506 or SDZ ASM 981.

5. A formulation according to any preceding claim wherein the permeation modulator is an alkanoic acid or alkenic acid.

6. A formulation according to claim 5 wherein the alkanoic acid or alkenic acid is selected from capric acid, octanoic acid, oleic such acid or acids of intermediate chain length.

7. A formulation according to any preceding claim wherein the dermatological condition is selected from psoriasis, alopecia, eczema dermatitis, lichen planus, lupus erthematosus, pyoderma gangrenosum, vitiligo, graft versus host disease, pustular skin infections, bacterial skin infections or acne vulgaris.

8. A formulation according to claim 7 wherein the dermatological condition is eczema dermatitis and the concentration of macrocyclic lactone antibiotic or immunosuppressive macrolide is 0.05% to 2% by weight.

9. A formulation according to any preceding claim wherein the permeation modulator is used in conjunction with a solvent system.

10. A formulation according to claim 9 wherein the solvent system comprises an aromatic alcohol or a biologically acceptable benzene derivative, with or without an admixture of monoglycerides and/or a fatty acid ester.

11. A formulation according to either claim 9 or 10 wherein the permeation modulator comprises capric acid and the solvent system comprises benzyl alcohol.

12. A formulation according to any of claims 8 to 11 wherein the concentration of the solvent system is 5% to 90% by weight.

13. A formulation according to any preceding claim further comprising a thickening agent.

14. A formulation according to claim 13 wherein the

thickening agent is selected from white soft paraffin, cetostearyl alcohol, yellow soft paraffin, cetyl alcohol, steryl alcohol, divalent carboxylic acid soaps and carnauber wax.

15. A topical formulation for the treatment of a dermatological condition which comprises an immunosuppressive macrolide or a pharmacologically active analogue, derivative or pro-drug thereof; characterized in that it further comprises a permeation modulator; and the permeation modulator and the macrolide or the pharmacologically active analogue, derivative or pro-drug thereof are present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

16. A formulation according to either claim 15 wherein the immunosuppressive macrolide is selected from sirolimus, FK506 or SDZ ASM 981.

17. A formulation according to claim 16 wherein the immunosuppressive macrolide is sirolimus.

18. The use in the manufacture of a topical composition for the treatment of a dermatological condition of a macrocyclic lactone antibiotic or an immunosuppressive macrolide or a pharmacologically acceptable analogue, derivative or pro-drug thereof characterised in that it further comprises a permeation modulator and the permeation modulator; the macrocyclic lactone antibiotic or the immunosuppressive macrolide or pharmacologically acceptable analogue, derivative or pro-drug thereof being present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

19. The use of claim 18 wherein the macrocyclic lactone antibiotic or immunosuppressive macrolide is present at up to 10% by weight of the composition.

20. The use of an immunosuppressant macrolide, a macrocyclic lactone antibiotic or a pharmacologically active analogue, derivative or pro-drug thereof in the preparation of a topical formulation as claimed in any one of claims 1 to 17.

21. A method for the treatment of a disease of the skin or muccosa which comprises applying thereto a topical composition comprising a macrocyclic lactone antibiotic or an immunosuppressive macrolide or a pharmacologically acceptable analogue, derivative or pro-drug thereof; characterised in that it further comprises a permeation modulator; and the permeation modulator, the macrocyclic lactone antibiotic or the immunosuppressive macrolide or pharmacologically acceptable analogue, derivative or pro-drug thereof is present in relative amounts such that when a therapeutic amount is applied to the skin a minimal systemic effect is produced.

22. A method according to claim 21 wherein the macrocyclic lactone antibiotic or immunosuppressive macrolide is present at up to 10% by weight of the composition.

23. A method according to claim 21 or 22 wherein the immunosuppressive macrolide is utilized.

Figure 1

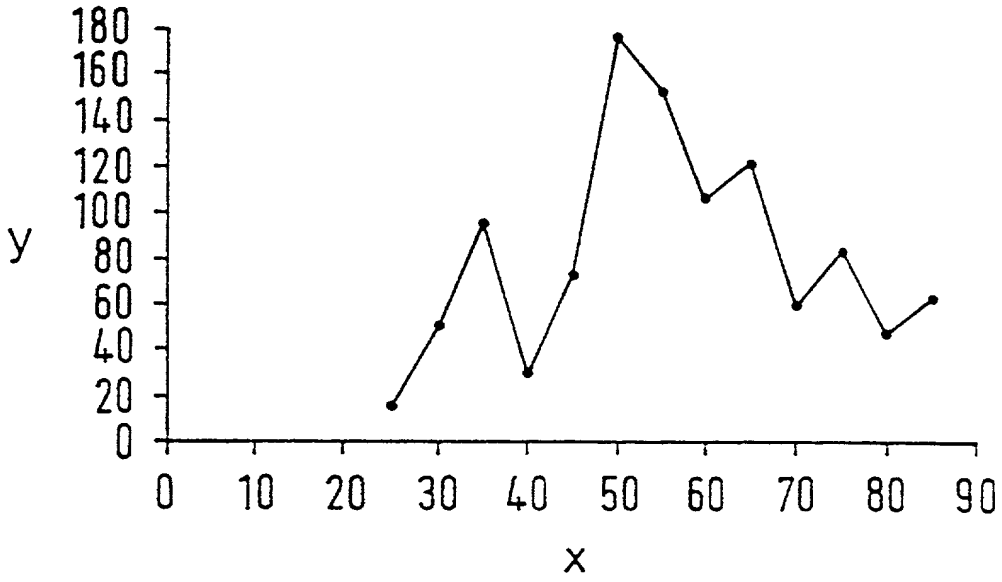


Figure 2

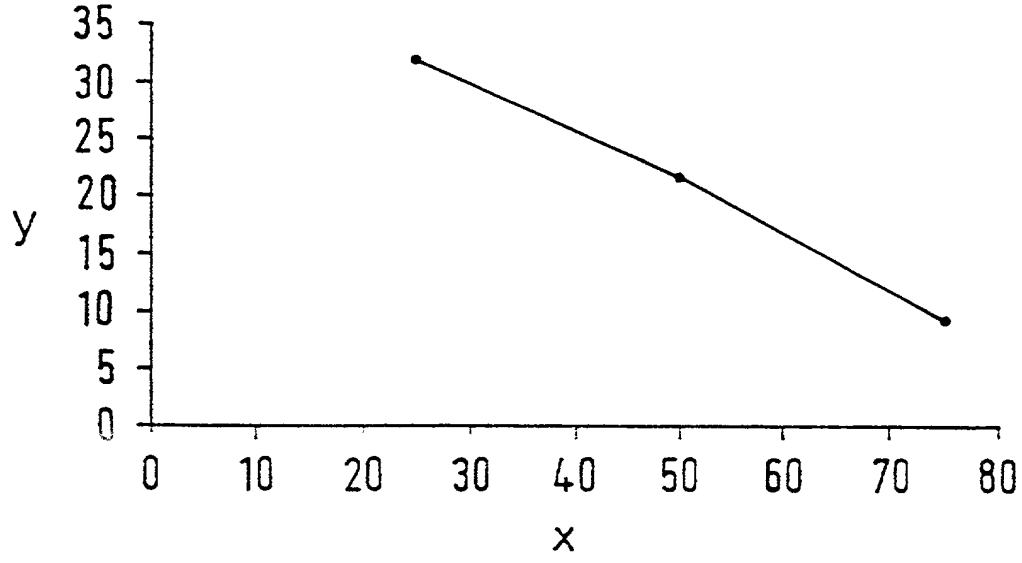


Figure 3

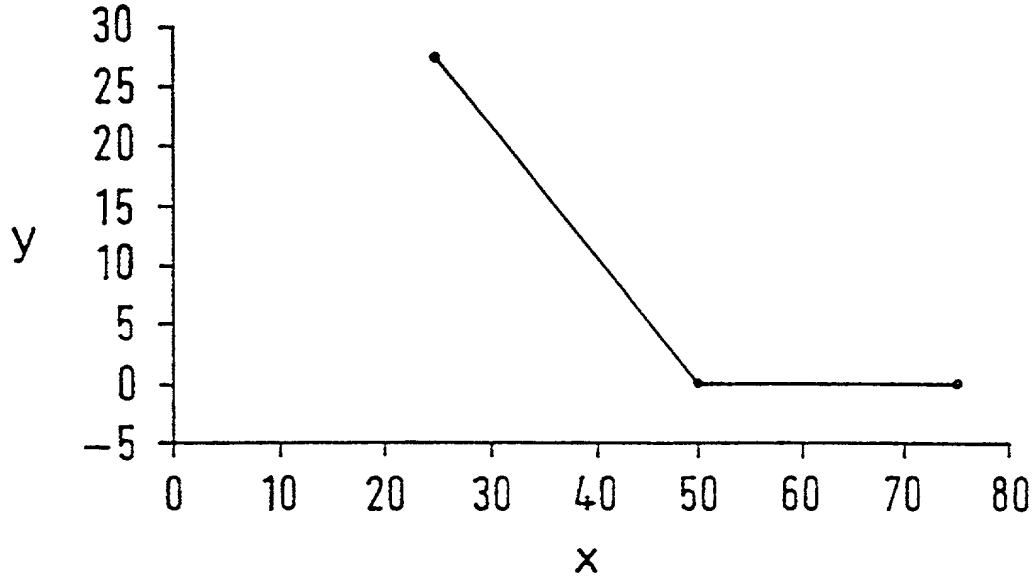


Figure 4

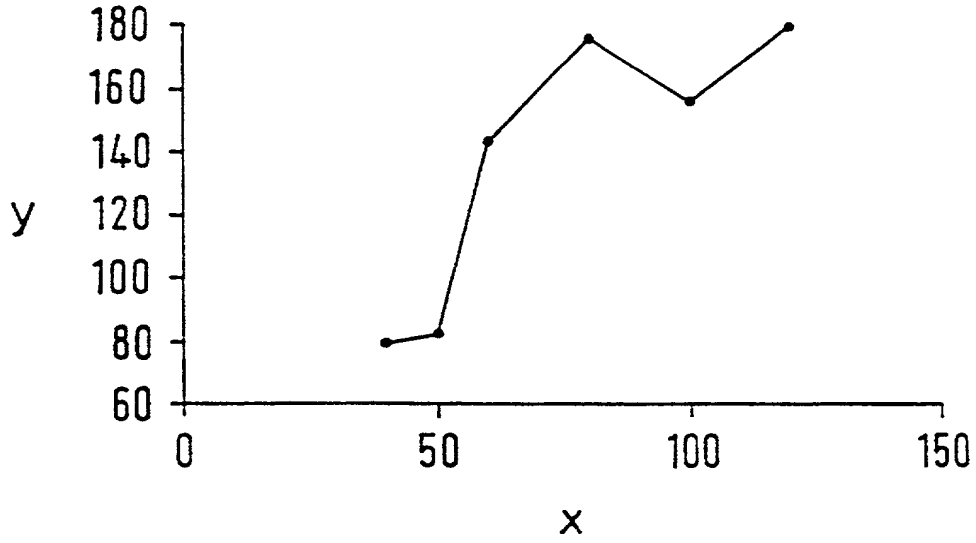


Figure 5

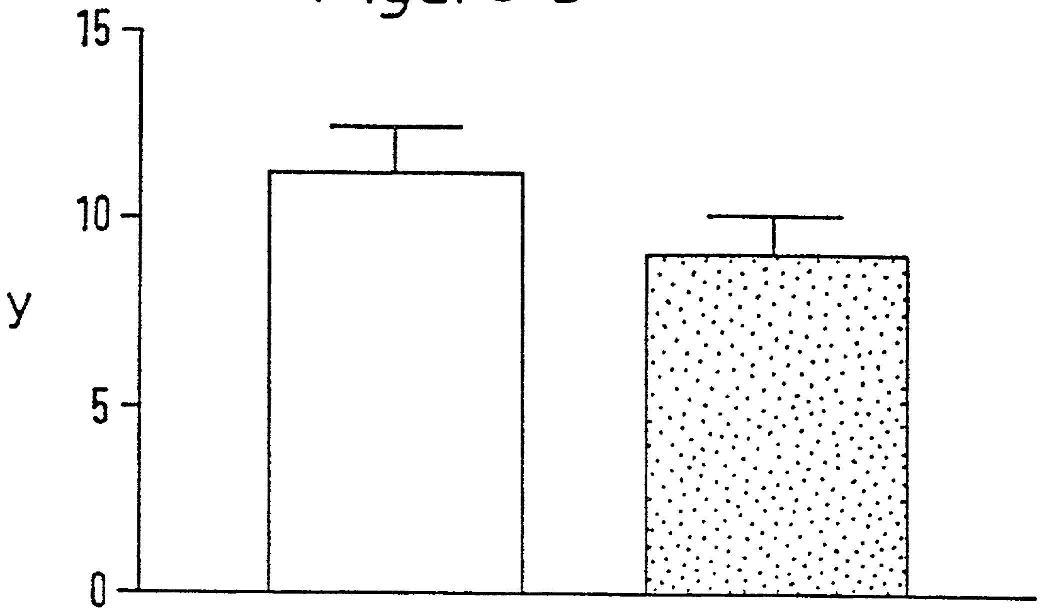
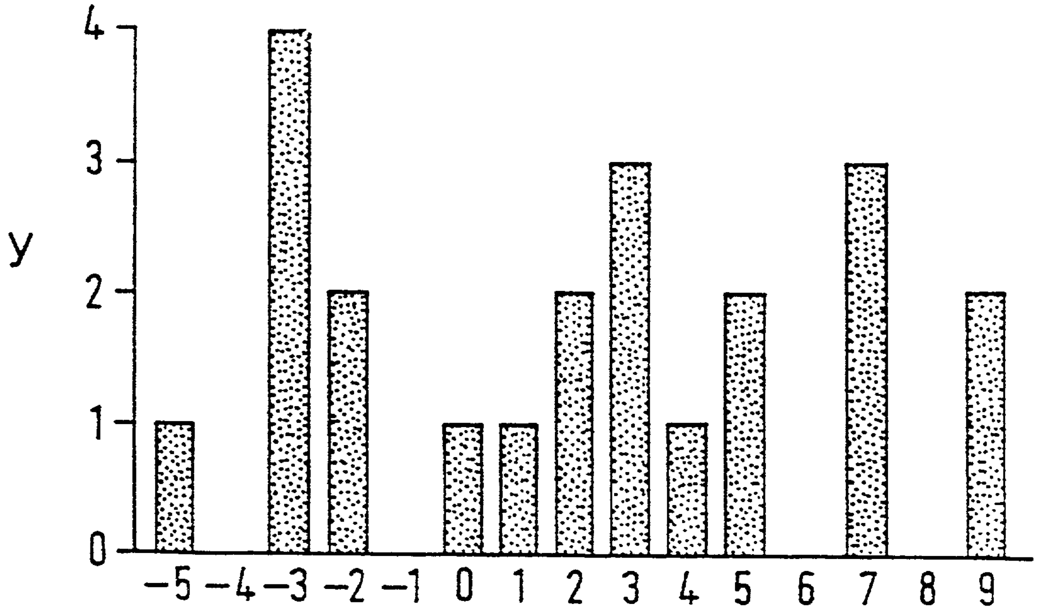


Figure 6



Attorney Docket No.: **ABLE-0014**

COMBINED DECLARATION AND POWER OF ATTORNEY

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name; and

I verily believe that I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled: **SKIN PENETRATION ENHANCING COMPONENTS** the specification of which:

( ) is attached hereto.

(XX) was filed on 5 November 1998 as Application Serial No. PCT/GB98/03317 and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to the patentability of this application in accordance with 37 CFR § 1.56.

I hereby claim foreign priority benefits under 35 U.S.C. § 119 of any foreign application(s) for patent or inventor's certificate listed below and have also identified below any foreign application for patent or inventor's certificate having a filing date before that of any application on which priority is claimed:

Country	Number	Date Filed	Priority Claimed			
Great Britain	9723669.9	7 Nov. 1997	Yes	X	No	
			Yes		No	

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s) listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose to the U.S. Patent and Trademark Office all information known to be material to patentability as defined in 37 CFR § 1.56 which became available between the filing date of the prior application and the national or PCT international filing date of this application:

Application Serial No.	Filing Date	Status (pending, patented)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith: **Jane Massey Licata**, Registration No. **32,257**, **Kathleen A. Tyrrell**, Registration No. **38,350**, and **Laura M. Plunkett**, Registration No. **45,015** of the firm of **Law Offices of Jane Massey Licata**, 66 East Main Street, Marlton, New Jersey 08053, and

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I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the

United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

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